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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,802	02/09/2004	Kari Alitalo	28967/34891.1	9059

4743 7590 10/09/2007

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
DANG, IAN D	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
10/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,802	ALITALO, KARI	
	Examiner	Art Unit	
	Ian Dang	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Following the decision of the petition filed on 05/23/2007, Groups 1-9, claims 43-80, and Groups 12-13, claims 85-93, are rejoined with Group 10, claims 81-84, already under examination. In addition, each the inhibitors is examined for the methods of Groups 1-13.

Status of Application, Amendments and/or Claims

The amendment of 23 March 2007 has been entered in full. Claims 1-42 have been cancelled and claims 94-96 have been added. Claims 43-96 are pending and under examination.

Claim Rejections - 35 USC § 112 (Second Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45, 49, 53, 58, 61, 67, 71, 81,85, 89, and 91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase " a polypeptide comprising an antigen binding fragment thereof " in claims 45, 49, 53, 58, 61, 67, 71, 81, 85, 89, and 91 is a relative term which renders the claims 45, 49, 53, 58, 61, 67, 71, 81,85, 89, and 91 indefinite. The term " a polypeptide comprising an antigen binding fragment thereof" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be

reasonably apprised of the scope of the invention. For instance, it is not clear as to what is the nature of the polypeptide and as to what is referred as antigen binding fragment.

Claims 43, 49, 50 and claims depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

The phrase "the function of Flt4 receptor tyrosine kinase" in claims 43, 49, and 50 is a relative phrase which renders the claims 43, 49, and 50 indefinite. The phrase "the function of Flt4 receptor tyrosine kinase" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For instance, it is not clear as to what functions of Flt4 receptor tyrosine kinase are encompassed in the above phrase and required for the claimed method.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 43-46 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,824,777. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are drawn to a method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism with a neoplastic disease.

Claim 43 is drawn to a method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism with a neoplastic disease, comprising the step of administering to said mammalian organism a composition, wherein said neoplastic disease is a breast carcinoma characterized by expression of Flt4 in vascular endothelial cells, wherein said composition comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vascular endothelial cells of said organism, and wherein said composition is administered in an amount effective to inhibit Flt4- mediated proliferation of said vascular endothelial cells, thereby inhibiting Flt4-mediated proliferation of said vascular endothelial cells.

Claim 1 of the reference patent (US patent No. 6,824,777) is drawn to a method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (a) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (b) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Specifically, claims 43-46 in the instant application and claims 1-5 of the reference patent are both directed to a method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism with a neoplastic disease. Among all the different limitations claimed in the instant application and in the reference patent a number of limitations are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the recited method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism with a neoplastic disease includes several embodiments (inhibitors) that would anticipate the limitations in claims 43-46. Claims 43-46 of the instant application listed above cannot be considered patentably distinct over claims 1-5 of the reference patent when there is specifically recited embodiment that would anticipate claims 43-46 of the instant application. Alternatively, claims 43-46 cannot be considered patentably distinct over claims 1-5 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 1-5 of that patent and falls within the scope of claims 43-46 herein because it would have been obvious to one having ordinary skill in the art to modify claims 1-5 of the reference by selecting a specifically disclosed embodiment that supports those claims.

Claims 49, 51, and 52 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 14 of U.S. Patent No. 6,824,777. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are drawn a method for antagonizing the function of Flt4 receptor tyrosine kinase (Flt4) in an organism that expresses Flt4.

Claim 49 is drawn to a method for antagonizing the function of Flt4 receptor tyrosine kinase (Flt4) in an organism, comprising a step of administering to the organism a composition comprising a polypeptide and a pharmaceutically acceptable carrier, wherein the polypeptide is

selected from the group consisting of: (a) an anti-Fit4 antibody or a polypeptide comprising an antigen binding fragment thereof; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof; (c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof; (d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and (e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent; and wherein the organism has a neoplastic disorder characterized by blood vessels comprising endothelial cells that express Flt4.

Claims 14-16 of the reference patent (US patent No. 6,824,777) is drawn to a method for antagonizing the function of Flt4 receptor tyrosine kinase (Flt4) in an organism that expresses Flt4, comprising a step of administering to the organism a composition comprising a soluble fragment of Flt4 in a pharmaceutically acceptable carrier, wherein the fragment binds to a Flt4 ligand.

Specifically, claims 49, 51, and 52 in the instant application and claims 14-16 of the reference patent are both directed to a method for antagonizing the function of Flt4 receptor tyrosine kinase (Flt4) in an organism. Among all the different limitations claimed in the instant application and in the reference patent a number of limitations are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the recited method for antagonizing the function of Flt4 receptor tyrosine kinase (Flt4) in an organism includes several embodiments (inhibitors) that would anticipate the limitations in claims 49, 51, and 52. Claims 49, 51, and 52 of the instant application listed above cannot be considered patentably distinct over claims 14-16 of the reference patent when there is specifically recited embodiment that would anticipate claims 49, 51, and 52 of the instant application. Alternatively,

claims 43-46 cannot be considered patentably distinct over claims 14-16 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 14-16 of that patent and falls within the scope of claims 49, 51, and 52 herein because it would have been obvious to one having ordinary skill in the art to modify claims 14-16 of the reference by selecting a specifically disclosed embodiment that supports those claims.

Claims 54-60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-31 of U.S. Patent No. 6,824,777. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are drawn to a method of inhibiting neoplastic cell growth in a mammalian subject.

Claim 54 is drawn to a method of inhibiting neoplastic cell growth in a mammalian subject, comprising steps of: (a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4; and
(b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells,
wherein said inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Claim 17 of the reference patent (US patent No. 6,824,777) is drawn to a method of inhibiting neoplastic cell growth in a mammalian subject, comprising steps of: (a) screening a mammalian subject to identify a neoplastic disorder characterized by cells expressing Flt4

receptor tyrosine kinase (Flt4); and (b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (i) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (ii) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Specifically, claims 54-60 in the instant application and claims 17-31 of the reference patent are both directed to a method of inhibiting neoplastic cell growth in a mammalian subject. Among all the different limitations claimed in the instant application and in the reference patent a number of limitations are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the recited method of inhibiting neoplastic cell growth in a mammalian subject (inhibitors) that would anticipate the limitations in claims 54-60. Claims 54-60 of the instant application listed above cannot be considered patentably distinct over claims 17-31 of the reference patent when there is specifically recited embodiment that would anticipate claims 54-60 of the instant application. Alternatively, claims 54-60 cannot be considered patentably distinct over claims 17-31 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 17-31 of that patent and falls within the scope of claims 54-60 herein because it would have been obvious to one having ordinary skill in the art to modify claims 17-31 of the reference by selecting a specifically disclosed embodiment that supports those claims.

Claims 61-64 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 32-37 of U.S. Patent No. 6,824,777. Although the

conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are drawn to a method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4).

Claim 61 is drawn to a method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising a step of administering to said mammal a composition, said composition comprising an inhibitor of binding between Flt4 ligand protein and Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function, wherein the inhibitor comprises a member selected from the group consisting of: (a) an anti-Fit4 antibody or a polypeptide comprising an antigen binding fragment thereof; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof; (c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof; (d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and (e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

Claim 62 is drawn to a method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising a step of administering to said mammal a composition, said composition comprising an inhibitor of binding between Flt4 ligand protein and Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Claim 32 of the reference patent (US patent No. 6,824,777) is drawn to a method of treating a mammal having breast cancer characterized by endothelial cells that express Flt4

tyrosine kinase (Flt4), comprising a step of administering to said mammal a composition, said composition comprising an inhibitor of binding between Flt4 ligand protein and Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function, wherein the inhibitor comprises a member selected from the group consisting of: (a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof; (c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof; and (d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21).

Specifically, claims 61-64 in the instant application and claims 32-37 of the reference patent are both directed to a method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4). Among all the different limitations claimed in the instant application and in the reference patent a number of limitations are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the recited a method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4) that would anticipate the limitations in claims 61-64. Claims 61-64 of the instant application listed above cannot be considered patentably distinct over claims 17-31 of the reference patent when there is specifically recited embodiment that would anticipate claims 61-64 of the instant application. Alternatively, claims 61-64 cannot be considered patentably distinct over claims 32-37 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 32-37 of that patent and falls within the scope of claims 61-64 herein because it would have been obvious to one having ordinary skill in the art to modify claims 32-37 of the reference by selecting a specifically disclosed embodiment that supports those claims.

Claims 71-76 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 38-49 of U.S. Patent No. 6,824,777. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are drawn to a method a method of inhibiting proliferation of blood vessel endothelial cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessel endothelial cells.

Claim 71 is drawn to a method of inhibiting proliferation of blood vessel endothelial cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessel endothelial cells, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vessel endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the blood vessel endothelial cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (a) an anti-Fit4 antibody or a polypeptide comprising an antigen binding fragment thereof; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof; (c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof; (d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and (e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

Claim 73 is drawn to a method of inhibiting proliferation of endothelial cells in a human organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in

endothelial cells, comprising the step of administering to said human organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in endothelial cells of said organism, thereby inhibiting Flt4- mediated proliferation of the cells, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Claim 38 of the reference patent (US patent No. 6,824,777) is drawn to a method of inhibiting proliferation of cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in cells, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (a) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (b) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Specifically, claims 71-76 in the instant application and claims 38-49 of the reference patent are both directed to a method of inhibiting proliferation of blood vessel endothelial cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessel endothelial cells. Among all the different limitations claimed in the instant application and in the reference patent a number of limitations are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the recited a method of inhibiting proliferation of blood vessel endothelial cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessel endothelial cells that would anticipate the limitations in claims 71-76. Claims 71-76 of the

instant application listed above cannot be considered patentably distinct over claims 38-49 of the reference patent when there is specifically recited embodiment that would anticipate claims 71-76 of the instant application. Alternatively, claims 71-76 cannot be considered patentably distinct over claims 38-49 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 38-49 of that patent and falls within the scope of claims 71-76 herein because it would have been obvious to one having ordinary skill in the art to modify claims 38-49 of the reference by selecting a specifically disclosed embodiment that supports those claims.

Claim Rejections - 35 USC § 112 (Written Description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-96 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 43, 53, 54, 61, 62, 71, 72, 73, 78, 81, 82, 85, 86, 89, 90, 92, and 94 are drawn to an inhibitor of the binding between Flt4 ligand protein and Flt4 having any structure. Claims 45, 49, 53, 58, 61, 67, 71, 81,85, 89, and 91 are drawn to any soluble polypeptide having any structure comprising any fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and a polypeptide comprising an Flt4

binding fragment of human prepro-VEGF-C (SEQ ID NO: 21). Claims 48, 50, 54, 57, 62, 68, 70, 72, 73, 75, 78, 80, 82, 86, 90 are drawn to a bispecific antibody or fragment thereof having any structure. Claims 46, 54, 68, 73, 78, 82, 86, 90, and 92 are drawn to a blood vascular endothelial marker.

For instance, the specification teaches that fragment of a molecule such as Flt4 protein is meant to refer to any portion of the molecule, such as the pep-tide core, or a variant of the peptide core (page 21, lines 21-23). In addition, the specification teaches that such putative inhibitors of Ftt4 and, in addition, antibodies against the Flt4 ligand, peptides or other compounds blocking Ftt4 receptor-ligand interaction, as well as antisense oligonucleotides complementary to the sequence of mRNA encoding the Flt4 ligand are useful in the regulation of endothelial cells and in the treatment of diseases associated with endothelial cell function (page 12, lines 5-9). Moreover, the specification teaches that a bispecific antibody recognizes an epitope (or epitopes) comprised of an Flt4/Flt4 ligand complex (e.g., a complex comprised of Fit4 bound to VEGF-C or VEGF-D) (page 16, lines 6-8). Finally, the specification teaches that by "blood vascular endothelial marker antigen" is meant any cell surface antigen that is expressed on proliferating vascular endothelial cells, and,
preferably, that is not expressed on lymphatic endothelial cells (page 15, lines 21-23).

Thus, the claims are genus claims. The specification and claims do not indicate what distinguishing structural attributes are shared by the members of the genus. Specifically, the specification does not clearly define the structure of an inhibitor of the binding between Flt4 ligand protein and Flt4, a soluble polypeptide comprising a fragment of Flt4 capable of binding to human VEGF-C (SEQ ID NO: 21), an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21), a bispecific antibody or fragment, a blood vascular endothelial marker and all methods of using such. Thus, the scope of the claims includes inhibitors and inhibitors

polypeptides having numerous structural variants, and the genus' are highly variant because there appears to be a significant number of structural differences between genus members. The specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish an inhibitor of the binding between Flt4 ligand protein and Flt4, a soluble polypeptide comprising a fragment of Flt4 capable of binding to human VEGF-C (SEQ ID NO: 21), an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21), a bispecific antibody or fragment, and a blood vascular endothelial marker are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, an inhibitor of the binding between Flt4 ligand protein and Flt4, a soluble polypeptide comprising a fragment of Flt4 capable of binding to human VEGF-C (SEQ ID NO: 21), an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21), a bispecific antibody or fragment, and a blood vascular endothelial marker are insufficient to describe the genus.

The written description requirement for a claimed genus' may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural features of the genus for an inhibitor of the binding between Flt4 ligand protein and Flt4, a soluble polypeptide comprising a fragment of Flt4 capable of binding

to human VEGF-C (SEQ ID NO: 21), an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21), a bispecific antibody or fragment, a blood vascular endothelial marker and all methods of using such.

There is no description of the special features, which are critical to the structure and function of the genus claimed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify an inhibitor of the binding between Flt4 ligand protein and Flt4, a soluble polypeptide comprising a fragment of Flt4, a bispecific antibody or fragment, and a blood vascular endothelial marker encompassed by the claims. Thus, no structural identifying characteristics or properties of the instant inhibitor of the binding between Flt4 ligand protein and Flt4, a soluble polypeptide comprising a fragment of Flt4 capable of binding to human VEGF-C (SEQ ID NO: 21), an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21), a bispecific antibody or fragment, and a blood vascular endothelial marker are provided such that one of skill would be able to predictably identify the encompassed variant biological and chemical entities recited in the methods of the instant claims. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

New Grounds of Rejections under *35 USC § 112 (Enablement)*

Applicant's response and arguments, see pages 18-20 of the response filed 03/23/2007, with respect to the rejection of claims 81-84 under 35 U.S.C. § 112, First paragraph, (Enablement) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection are made for

claims 81-84 of Group X. The rejection of claims 81-84 of Group X has been added to the rejection regarding claims 43-80, Groups I-IX, and claims 85-93, Groups XII-XIII.

Claim Rejections - 35 USC § 112 (Enablement)

Claims 43-96 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breath of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

Nature of the invention and breath of the claims

The invention is drawn to a method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism. The invention is broad because the recitation of claims encompasses the use of a large number of inhibitors of the binding between Flt4 ligand protein and Flt4, such as, antibodies against VEGF-C or VEGF-D, soluble polypeptides comprising a fragment of Flt4 capable of binding to human VEGF-C (SEQ ID NO: 21), Flt4 binding fragments of human prepro-VEGF-C (SEQ ID NO: 21), a bispecific antibody or fragments, and blood vascular endothelial markers.

For instance, the specification teaches that fragment of a molecule such as Flt4 protein is meant to refer to any portion of the molecule, such as the pep-tide core, or a variant of the peptide core (page 21, lines 21-23). In addition, the specification teaches that such putative inhibitors of Flt4 in addition to antibodies against the Flt4 ligand, peptides or other compounds blocking Ftt4 receptor-ligand interaction, as well as antisense oligonucleotides complementary to the sequence of mRNA encoding the Flt4 ligand are useful in the regulation of endothelial cells and in the treatment of diseases associated with endothelial cell function (page 12, lines 5-9). Moreover, the specification teaches that a bispecific antibody recognizes an epitope (or epitopes) comprised of an Flt4/Flt4 ligand complex (e.g., a complex comprised of Fit4 bound to VEGF-C or VEGF-D) (page 16, lines 6-8). Finally, the specification teaches that by "blood vascular endothelial marker antigen" is meant any cell surface antigen that is expressed on proliferating vascular endothelial cells, and, preferably, that is not expressed on lymphatic endothelial cells (page 15, lines 21-23).

Unpredictability and state of the art

The state of the art for an antibody to Flt4 as an inhibitor of Flt4 function has been established, but other inhibitors of Flt4 has not been established at this point.

At page 20 of the response filed 03/23/2007, Applicant indicates that the reference by Laakkonen et al. (2007) recites that the blood vessel density of tumors treated with an anti-VEGFR-3 antibody was significantly decreased when compared with blood vessel density of tumors treated with the control antibody. Furthermore, when the effect of an VEGFR-3 antibody in the early phases on tumor growth was studied, results indicated that inhibition of tumor growth was already evident after four injections of the VEGFR-3 antibody.

Although the state of the art for an antibody against Ft4 is well characterized, other inhibitors of Flt4, such as antibodies against VEGF-C or VEGF-D, soluble polypeptides

fragments of Flt4 capable of binding to human VEGF-C (SEQ ID NO: 21) or Flt4 binding fragments of human prepro-VEGF-C (SEQ ID NO: 21) are still under development. For instance, the recent publication by Karponen et al., (2006, The American Journal of Pathology, Volume 169, Number 2, pages 708-718) teaches that the blocking of VEGF-C and VEGF-D should be safe method to inhibit metastasis because normal lymphatic vessels are not affected by such treatment in the adults (page 718, right column, last paragraph). Thus the inhibition of Flt-4 function with antibodies against VEGF-C or VEGF-D remains to be established.

In view of these teachings in the art and the limited guidance provided in the specification, the Flt4 inhibitor Flt4 antibody is not predictable for all inhibitors of Flt4, such as antibodies against VEGF-C or VEGF-D, soluble polypeptides fragments of Flt4 capable of binding to human VEGF-C (SEQ ID NO: 21), or Flt4 binding fragments of human prepro-VEGF-C (SEQ ID NO: 21).

The amount of direction or guidance present

Applicants' disclosure is limited to the anti-Flt4 antibody. However, the specification does not provide guidance regarding the identifying characteristics of inhibitors of the binding between Flt4 ligand protein and Flt4, such as antibodies against VEGF-C or VEGF-D, soluble polypeptides fragments of Flt4 capable of binding to human VEGF-C (SEQ ID NO: 21), the Flt4 binding fragments of human prepro-VEGF-C (SEQ ID NO: 21), the bispecific antibody or fragments, and the blood vascular endothelial markers. For instance, there is no guidance regarding the structural features of the inhibitors that are required to inhibit the binding between Flt4 ligand protein and Flt4. In addition, the specification does not provide any guidance regarding any identifying structural characteristics of the Flt4 fragments capable of binding to VEGFC, such as a conserved region or lengths of the fragments in order to make and use such

inhibitor in the claimed method. Moreover, the specification does not provide guidance regarding the epitopes for the antibodies for VEGF-C or VEGF-D.

Without specific guidance one of ordinary skill in the art would be subject to undue experimentation in order to make and use the encompassed inhibitors.

Working Examples

Although Applicants have provided an example for an anti-Flt4 antibody (Example 26, page 64; Example 28, page 79) and an example for the blood vascular endothelial marker PAL-E (Figure 5, page 18), the specification does not provide any methods or working examples for any other inhibitors of the binding between Flt4 ligand protein and Flt4, any antibodies against VEGF-C or VEGF-D, any soluble polypeptides comprising a fragment of Flt4 capable of binding to human VEGF-C (SEQ ID NO: 21), any Flt4 binding fragments of human prepro-VEGF-C (SEQ ID NO: 21), any bispecific antibody or fragments, and any other blood vascular endothelial markers.

The quantity of experimentation needed

Without sufficient disclosure in the specification it would require undue experimentation to practice the invention commensurate in scope with the claims because, the claims are broadly drawn to any inhibitors of the binding between Flt4 ligand protein and Flt4, usch as any antibodies against VEGF-C or VEGF-D, any soluble polypeptides comprising a fragment of Flt4 capable of binding to human VEGF-C (SEQ ID NO: 21), any Flt4 binding fragments of human prepro-VEGF-C (SEQ ID NO: 21), any bispecific antibody or fragments, and any blood vascular endothelial markers. A large amount of experimentation is required for one of skill in the art to be able to determine the inhibitors of the binding between Flt4 ligand protein and Flt4, such as antibodies against VEGF-C or VEGF-D, soluble polypeptides fragments of Flt4 capable of

binding to human VEGF-C (SEQ ID NO: 21), Flt4 binding fragments of human prepro-VEGF-C (SEQ ID NO: 21), bispecific antibody or fragments, and the blood vascular endothelial markers in order to make/use the claimed methods of the instant application.

Conclusion

No claim is allowed.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Ian Dang
Patent Examiner
Art Unit 1647
September 28, 2007

MANJUNATH N. RAO, PH.D.
Supv. PRIMARY EXAMINER
TECH. CTR. 1647